REMARKS/ARGUMENTS

Applicant would like to thank the Examiner for the careful consideration given the present application. The application has been carefully reviewed in light of the Office Action and amended as deemed necessary and appropriate to secure allowance of the claims.

Specifically, by this Amendment the specification and claims 1, 3-5, 11-17, 23-26, 28, 36 and 40-42 have been amended, claims 2, 10, 18-22, 27, 38 and 43 have been canceled and new claims 44-46 have been added to the application. Accordingly, claims 1, 2-9, 11-17, 23-26, 28-37, 39-42 and 44-46 are pending in the application, with claims 23-25 having previously been withdrawn from consideration. No new matter has been added to the application.

In the prior Office Action, the Examiner acknowledged applicant's prior election of levobupivacaine as the neurotoxic substance and glycerin as the biocompatible solvent, but indicated that the search was expanded to include other "amide local anesthetics". The Examiner withdrew claims 23-25 and 27 from consideration as being drawn to non-elected subject matter and requested correction of the spelling of the word "adrenaline" in claim 36. By this Amendment, non-elected claim 27 has been canceled and the spelling of adrenaline in claim 36 has been corrected, as requested. In addition, applicant amended the specification to make reference to the international application, as requested.

The Examiner indicated that the listing of references in the Search Report was not considered to be an Information Disclosure Statement in compliance with 37 C.F.R. §1.98. Applicants note that an English translation of the Search Report was

furnished for the convenience of the Examiner and was not intended to be an Information Disclosure Statement in compliance with 37 C.F.R. §1.98.

In the prior Office Action, the Examiner rejected claims 1-37 and 39-42 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that it was not clear what was contemplated by the phrase "neurotoxic substance". By this Amendment, applicant has amended claims 1 and 40 to clarify that the neurotoxic substance is an "amide local anesthetic". This terminology, which was used by the Examiner in the Office Action, is well known in the art. Local anesthetics are classified as either "amide local anesthetics" or "ester local anesthetics". The amendments to claims 1 and 40 clearly make the composition of the "neurotoxic substance" definite.

The Examiner also rejected claims 20-22 under 35 U.S.C. §112, second paragraph, as being indefinite for including the phrase "another substituted tetracaine". Inasmuch as tetracaine is an "ester local anesthetic" and not an "amide local anesthetic", claims 20-22 have been canceled, thereby rendering the prior rejection thereof moot.

Claim 28 was also rejected under 35 U.S.C. §112, second paragraph, as being indefinite due to the inclusion of the phrase "derivatives inclusive of analogues". In accordance with the Examiner's suggestion, this phrase has been removed from claim 28. In view of the claim amendments made herein, applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Also in the prior Office Action, the Examiner rejected claims 1-22, 14, 26, and 40-42 under 35 U.S.C. §103(a) as being unpatentable over Milligan et al. (Anaesthesia 1998, 43, 563-564) in view of Bawa et al. (U.S. Pat. 6,261,547), Goldenheim et al. (U.S. Pat. 6,248,345) and Arias-Alvarez (U.S. Pat. 4,657,764). For the reasons set forth below, applicant respectfully submits that the claims, as amended herein, are clearly patentable over Milligan et al., Bawa et al., Goldenheim et al. and Arias-Alvarez. Reconsideration is therefore respectfully requested.

Milligan et al. discloses a double-blind study in which doses of 0.25% and 0.5% bupivacaine were injected into the knee joint after arthroscopy. Milligan et al. report in the summary that "intra-articular bupivacaine had no significant (post operative) analgesic effect in either concentration". In the discussion section, Milligan et al. note that the plasma levels were all determined to be below toxic plasma bupivacaine concentrations in man. They stated that while this might support a case for the use of higher concentrations of bupivacaine, they did not propose to undertake such a study for two reasons: (1) the bupivacaine molecules would likely traverse the synovium rapidly and thus cause plasma concentrations to increase (implying, of course, that there would be an increased risk that systemically toxic concentrations could be achieved in the plasma); and (2) it would not likely be effective because the lack of any significant analgesic effect suggested that the source of pain after arthroscopy was outside the capsule of the knee joint.

The Examiner contends in the prior Office Action that since claim 1 did not provide a concentration of the neurotoxic substance that would entail neurolysis, any concentration would do so. However, this contention is clearly contradicted by the results reported in Milligan et al. The relatively low concentrations of bupivacaine

used by Milligan et al. were clearly not sufficient to entail neurolysis, because no long-term analgesic effect was observed. Thus, the Examiner's assertion that "any concentration would do so" is absolutely contradicted by the findings reported in Milligan et al. Applicants further note that claim 1 has been amended to clarify that the neurotoxic substance (i.e., the "amide local anesthetic") is present in the agent for treating joint pain in a concentration whereby the agent for treating joint pain is predominantly toxic to nociceptive nerve fibers but not systemically toxic when injected into a post-operative joint space. Thus, claim 1 now provides a that the agent comprises a concentration of the neurotoxic substance that would entail neurolysis.

The Examiner contends that in view of Milligan et al., one of ordinary skill in the art would have been motivated to inject bupivacaine into a post-operative joint space at higher concentrations because Milligan et al. teach that a concentration of 0.5% provided little analgesia and because Milligan et al. noted that in view of the plasma levels, a case could be made for the use of higher concentrations. But this contention runs contrary to the clear teaching of Milligan et al. Milligan et al. does not suggest that one should use higher concentrations of bupivacaine to achieve a long-term analgesic effect. On the contrary, Milligan et al. expressly teaches away from injecting higher concentrations of bupivacaine into the post-operative joint space (1) because of the potential that the plasma concentration would increase rapidly (i.e., to systemically toxic levels) and (2) because the source of post arthroscopy joint pain is likely outside the capsule of the knee joint. Thus, no person of ordinary skill in the art would be motivated by the teachings of Milligan et al. to

inject bupivacaine at a higher concentration into the post-operative joint, and would not have had any expectation that doing so would produce any beneficial effect.

Applicant readily acknowledges that both amide and ester local anesthetics are known to relieve pain locally almost anywhere in the body for some hours. Such compounds reversibly block the ion channels at the nerve's surface. But this effect is also known to subside, either by chemical degradation of the anesthetic or by replacement of the ion channels by the nerve. It is also known that the analgesic effect may be somewhat extended by administering a greater doses or through the use of a formulation that sustain a gradual release of the anesthetics. This has been known for a long time and is of course not new.

However, the surprising and new effect that applicant discovered and now claims is that when amide local anesthetics are injected into a post-operative joint space at an appropriately high concentration, a totally new mode of pharmaceutical action may be achieved. Applicant has surprisingly discovered that at sufficiently high concentrations, amide local anesthetics destroy the sensitive nerves selectively and irreversibly, which results in permanent de-nervation ("neurolysis"), which thus provides an analgesic effect that lasts for months to years, rather than a few hours or a day as one of ordinary skill in the art would expect. The present invention is in no way related to a sustained release mechanism. The fact that applicant's discovery is nowhere described in the literature, foreseen or hinted for postoperative pain relief, despite its very useful clinical benefit, underlines its inventiveness.

Applicant's invention is not simply a matter of routine optimization, as has been suggested by the Examiner. One of skill in the art, particularly upon consideration of the teachings of Milligan et al., would conclude that injections of

amide local anesthetics into the post-operative joint space would not provide any significant analgesic effect, even at elevated concentrations, because Milligan et al. suggest that the source of pain after arthroscopy is outside the capsule of the knee joint. Applicant's invention, as claimed, claims a method for treating post-operative joint pain that uses amide local anesthetics in an entirely different way and for an entirely different purpose than previously known in the art.

The references the Examiner attempts to combine with Milligan et al. (Bawa et al., Goldenheim et al. and Arias-Alvarez) do not overcome the deficiencies noted in the teachings set forth in Milligan et al. None of these references suggest injecting concentrations of amide local anesthetics into post-operative joint spaces sufficient to entail neurolysis. Bawa et al. relates to an ophthalmic composition, which is an external optical application of an anesthetic drug to the eye. The mechanism employed in Bawa et al. is not neurolysis, but rather it is sustained release. It is wholly inapposite.

Goldenheim et al. discloses the use of local anesthetics in joints, but again does not disclose or suggest the use of neurotoxic concentrations of local anesthetics for any beneficial purpose. Goldenheim et al. discloses a sustained release composition. Again, the mechanism would be the same analgesia as commonly produced through the use of local anesthetics, and not neurolysis.

Arias-Alvarez only relates to the use of sodium bisulphate, which is addressed only in a dependent claim. Arias-Alvarez cannot be relied upon to cure the deficiencies in the teachings of Milligan et al.

The Examiner also rejected claims 1-8, 10, 11, 13, 26, 28, 35 and 40-42 under 35 U.S.C. §103(a) as being unpatentable over Macek et al. (U.S. Pat.

3,368,937). Macek et al. discloses an injectable steroid solution comprising an anti-inflammatory steroid and a local anesthetic. Macek et al. teach that the steroid solution can be administered by intramuscular, intrasynovial, intra-articular and soft-tissue injection. Clearly, the concentration of local anesthetic in the steroid solutions according to Macek et al. do not make them predominantly toxic to nociceptive nerve fibers, and thus would not be of a sufficient concentration to entail neurolysis. If that were the case, one can only imagine the problems that would follow subsequent to intramuscular administration of the composition, which is expressly suggested by Macek et al..

Like Milligan et al., Macek et al. clearly does not teach or suggest applicant's surprising method of treating post-operative joint pain. Macek et al. does not appreciate that amide local anesthetics, when injected into the joint space at appropriate concentrations, can entail neurolysis that provides a long-lasting (months to years) analgesic effect. This is not suggested by Macek et al. And one having ordinary skill in the art would not have been motivated to arrive at applicant's method, as claimed, in view of the teachings of Macek et al. Macek et al. teaches one how to combine a steroid with a local anesthetic in a concentration well-below where neurolysis would occur, such that the steroid solution is quick-acting and exhibits a long shelf-life.

Finally, the Examiner rejected claims 1, 2, 5, 28-37 and 39 under 35 U.S.C. §103(a) as being unpatentable over Macek et al. in view of Goldenheim et al., and with respect to claims 34 and 37 in view of Davis et al. (U.S. Pat. 3,917,830), and with respect to claim 39 in view of Herschler (U.S. Pat. 4,296,104), and with respect to claims 28-30 in view of Oakes et al. (U.S. Pat. 5,061,485) and with respect to

claims 31 and 32 in view of Mueller (U.S. Pat. 5,002,761) and with respect to claim 36 in view of Chasin et al. (U.S. Pat. 5,942,241), and with respect to claim 33 in view of Klaveness (U.S. Pat. 5,242,683). Macek et al. and Goldenheim et al. have been discussed above. Neither reference fairly teaches injecting an agent comprising an amide local anesthetic in a concentration sufficient to cause neurolysis into the post-operative joint space for the purpose of achieving an analgesic effect lasting for many months to years. Both references teach injecting local anesthetics into joint spaces, but only in concentrations that would produce the known and expected short-term analgesic effect. Macek et al. teaches one skilled in the art how to prepare a steroid/local anesthetic composition that is quick-acting and has a long shelf life. Goldenheim et al. teaches one skilled in the art how to prepare a sustained release anesthetic formulation. But neither fairly teach or suggest applicant's invention, which is a method of treating post-operative joint pain via the injection of an agent containing an amide local anesthetic in a concentration whereby neurolysis is effected. Applicant's discovery is not a matter of routine optimization inasmuch as it uses an entirely different mechanism than has been used in the past. In view of the claim amendments and for the reasons set forth herein, applicant respectfully submits that the rejections under 35 U.S.C. §103(a) should be withdrawn.

Also in the prior Office Action, the Examiner provisionally rejected claims 1, 2, and 40-42 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 50 and 51 of copending App. Ser. No. 11/722,779. The Examiner also provisionally rejected the same claims on the same grounds as being unpatentable over claims 39-42 of copending App. Ser. No. 11/722,857 and

claims 94-96 of App. Ser. No. 11/722,484. Applicant respectfully requests reconsideration of the provisional rejections in view of the amendments made to claims 1 and 40 herein, which distinguish the invention from the inventions claimed in the co-pending applications.

In light of the foregoing, it is respectfully submitted that the present application is in a condition for allowance and notice to that effect is hereby requested. If it is determined that the application is not in a condition for allowance, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge same to our Deposit Account No. 18-0160, our Order No. LUS-15874.

Respectfully submitted,

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